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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,686	12/17/2001	Roger Y. Tsien	REGEN1270-5	4319

25213 7590 03/08/2004

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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,686	TSIEN ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after NON-final rejection. Since this application is NOT eligible for continued examination under 37 CFR 1.114 because the last Office action mailed August 20, 2003 was non-final rejection, Applicant's submission filed on December 19, 2003 has NOT been entered.

The amendment filed December 19, 2003 amending the specification to insert references to the sequence identifiers and correct typographical errors, amending claims 1, 2, 8 and 13 and canceling claims 16-23 has been entered.

The Sequence Listing and the computer readable form thereof filed December 19, 2003 have been entered.

Claims 1-15 are pending.

Terminal Disclaimer

The terminal disclaimer filed on December 19, 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 5,777,079 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on December 19, 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 6,066,476 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 8 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a modified form of an *Aequorea* wild-type GFP having a different excitation and/or emission spectrum from the wild type GFP wherein said modified form of an Aequorea wild-type GFP is at least 95% homologous to the amino acid sequence of SEQ ID NO:2. Claim 2 depends from claim 1 and limits the property to "an alteration in the ratio of two main excitation peaks relative to the wild type GFP". Claims 3 and 5 depend from 2 and recite "two main excitation peaks" with increased fluorescence exhibited at a shorter-wavelength peak and longer-wavelength peak, respectively, of the two main excitation peaks. Claim 8 depends from claim 1 is drawn to "the fluorescent product [that] fluoresces at a shorter wavelength than the corresponding product derived from wild–type GFP". Claim 13 depends from claim 1 and is drawn to "the fluorescent product [that] exhibits emission relative to the corresponding product of wild–type GFP".

While the claims limit the structure of a modified GFP as being at least 95% homologous to SEQ ID NO:2, they do not correlate said structure with a specific function. With regard to claim 1, the claimed modified GFP can have undefined number of excitation and/or emission peaks at any wavelength and different intensity of emission. The dependent claims similarly encompass diverse extremely broadly defined fluorescent properties.

The specification teaches that mutations within less than 3% of SEQ ID NO:2 can lead to diverse fluorescent properties. The correlation between the structures and imparted functions is unpredictable. The relevant mutants have been found empirically. For each of claims 3, 5, 8 and 13, the specification teaches an example of a modified GFP mutated at the specific positions of SEQ ID NO:2 having a specific fluorescent property. However, the specification does not teach a modified GFP with a requisite fluorescent properties exhibited by a modified GFP mutated at positions other than those empirically found by inventors.

For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only several species within the genus wherein the correlation between the structure and function (fluorescent characteristics) is neither known in the art nor disclosed by the specification.

Thus, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one

skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 1-3, 5, 8 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified GFP comprising the mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I and having an amino acid sequence at least 95% homologous to SEQ ID NO: 2 and the specific fluorescent properties, does not reasonably provide enablement for a modified *Aequorea* GFP having any amino acid sequence at least 95% homologous to SEQ ID NO: 2 and having a fluorescent function or a modified *Aequorea* GFP having any amino acid sequence at least 95% homologous to SEQ ID NO: 2 comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I and having any undefined fluorescent function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 5, 8 and 13 recite a modified *Aequorea* GFP comprising the amino acid sequence at least 95% homologous to SEQ ID NO:2 having indefinitely diverse fluorescent properties. The specification teaches modified GFPs having amino acid sequences that differ from SEQ ID NO:2 by specific mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I and having specific fluorescent properties. The specification enables for modified GFPs having an amino sequence at least 95% homologous to SEQ ID NO:2 comprising the specific mutations and having the specific fluorescent properties. However, the specification does not support the broad scope of the claims which encompass modified GFPs having an amino sequence at least 95% homologous to SEQ ID NO:2 comprising or not comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I, wherein said modified GFPs have no specific fluorescent property, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a

rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into, add to or delete from the known sequence), changes in amino acid residues will result in a desired biological activity. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in a certain activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited.

Furthermore, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure.

Therefore, one of ordinary skill in the art would require guidance, beyond that provided, in order to make a modified GFP having an amino acid sequence at least 95% homologous to SEQ ID NO:2 comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I and having fluorescent properties other than exhibited by the disclosed mutants in a manner reasonably correlated with the scope of the claims. Furthermore, one of ordinary skill in

the art would require guidance, beyond that provided, in order to use a modified GFP having an amino acid sequence at least 95 % homologous to SEQ ID NO:2 comprising mutations S202F/T203I, I167V/T, S65T/M153A/K238E, Y66F/H/W, Y66H/Y145F, Y66W/N146I/M153T/V163A/N212K, Y66W/I123V/Y145H/H148R/M153T/V163A/N212K or S65A/C/T/L/V/I or not comprising said mutations and having no specific fluorescent properties in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, with dependent claims 2-15, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The wording of Claim 1 is confusing because of the following. It recites "a modified form of an *Aequorea* wild-type GFP" and "a fluorescent product" formed therefrom. The difference in scope between the two terms, "a modified form of an *Aequorea* wild-type GFP" and "a fluorescent product formed therefrom" is unclear. Further, it unclear which products other than the wild-type GFP are encompassed by the term "a corresponding product of the wild-type GFP". Deletion of term "product" or "corresponding product' is suggested. With regard to claim 3, it is unclear whether "the two main excitation peaks" of the wild-type GFP are implied or modified GFP may have any two excitation peaks. Regarding claim 8, the metes and bonds of the term "derived" are defined neither in the specification nor the art rendering the claim unclear.

Allowable Subject Matter

Claims 4, 6, 7, 9-12, 14 and 15 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed December 19, 2003 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, written description rejection, Applicants argue that the modified GFP is characterized by structure (95% homology to SEQ ID NO:2) and by function because the claims recite "a fluorescent product exhibiting a different excitation and/or emission spectrum from a corresponding product of the wild-type GFP polypeptide sequence" (Remarks, page 9). This is not persuasive because as explained above, there is no specific defined function and specific fluorescent properties of a modified GFP are not recited.

With regard to the 112, 1st paragraph, enablement rejection, Applicants argue that "the specification being enabling for a modified GFP comprising the amino acid sequence that differs from SEQ ID NO;2 by specified mutations, and being enabling for a modified GFP that differs from SEQ ID NO:2 by less than 5% as measured by amino acid sequence homology" (page 11). This is not persuasive with regard to the entire scope because as explained above, the specification is enabling for a modified GFP comprising the specific mutations and having an amino acid sequence at least 95%

homologous to SEQ ID NO:2 and having the specific fluorescent function. Applicants further argue that "Applicants disclose that there is "surprising tolerance for substitution" at Tyr 66(page 7, paragraph 27) and other substitutions of the sequence. Thus, the specification does establish the regions of the protein structure which may be modified without effecting the requisite activity, the general tolerance to modification" (Remarks, pages 10-11). This is not persuasive, because modified GFPs comprising mutations at position 66 and retaining the specific fluorescent function are not rejected.

Other outstanding rejections and objections are moot in view of the amendment and TDs.

Conclusion

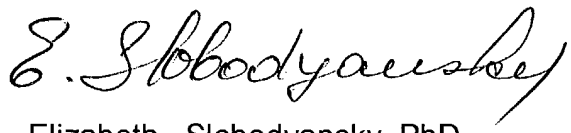
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

March 3, 2004